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ON 9 August 2004
ATTORNEY FOR APPLICANT
9 August 2004
DATE

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PATENT & TRADEMARK OFFICE
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Attorney Docket No. P50383D2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Burch	9 August 2004
Serial No.:	10/719,211	Previous Art Unit.: 1614
Filed:	21 November 2003	Previous Examiner: D. Jagoe
For:	PHARMACEUTICAL FORMULATION	

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION UNDER 35 CFR §1.181

Dear Sir:

This letter is in response to the "Notice of Incomplete Nonprovisional Application" filed under 37 CFR 1.53(b) which was mailed 27 May 2004, and which includes a two month

The history of the application is as follows:

The Parent application 09/788,948 from which this claims priority, is the §371 national stage entry of PCT/US96/14554. This application has been accorded a US filing date of 20 February 2001.

On 21 November 2003, Applicants submitted by Express Mail a divisional application claiming benefit from the above noted parent US application and enclosed therewith a transmittal sheet for the filing of a Utility application, a declaration/power of attorney, a postcard, a copy of the PCT specification (WO 97/09042), an abstract, an Information Disclosure Statement, PTOL 1449 forms and cited references, and a preliminary amendment. Applicants have received the return postcard and Applicants have the original Express Mail Customer Copy, date stamped accordingly.

Accordingly, Applicants submit for the Commissioners review photocopies of the entire submittal of 21 November 2003. Applicant's attorney hereby stated that the enclosed copy of the WIPO specification is a true copy of the original WIPO specification as filed in this application (and in the parent application), with Applicants transmittal letter of 21 November 2003. A newly executed oath or declaration is not believed to be necessary as this is the submittal of a divisional application using the same declaration as submitted during the course of prosecution of Applicants parent application and which has met all necessary requirements therein. No new fees are believed due. However, if the $130.00 petition fee or any additional fees or charges are believed required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

If any additional information is believed necessary for a resolution of this problem, the Commissioner is requested to contact the undersigned at the number indicated below.

Respectfully submitted,

Dara L. Dinner
Attorney for Applicant
Registration No. 33,680

GLAXOSMITHKLINE
Corporate Intellectual Property UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-5017
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P50383D2

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'MAILING: CERTIFICATE/ EXPRESS MAIL # EV 349425397US

U.S. Serial No.: _____ Filing Date: _____
Int'l App. No.: _____ Int'l Filing Date: _____

RECEIPT IS ACKNOWLEDGED FOR THE FOLLOWING:

- ☒ Appln. Trans. (+ 1 copy) for: ☐ Provisional ☐ CIP ☐ Statement to Support Filing
- ☐ Utility/Continuation ☐ CPA ☐ RCE ☒ Divisional ☐ Copy of Notice to Comply
- ☒ Specification 11 pages ☒ Abstract 1 pgs ☐ Diskette ☐ Paper Seq.Listin
- ☒ Dec. & Power of Atty 3 pages ( ) ☐ Appeal Brief ____ pages
- ☒ Drawings 3 Sheet(s)/Figs 1 to 3 ☐ Petition ___ pgs.
- ☐ Assignment ___ pages & Recordation Cover Sheet ☐ Status Request
- ☐ Trans. Ltr Natl Stage Entry (3pgs.) ☐ Trans. Nat'l Stage (2nd sub)
- ☐ Information Disclosure Statement ☐ Resp. to Writtten Opinion
- ☒ Form PTO-1449 7 pgs. & 132 References ☐ Priority Document
- ☒ Amendment ☐ Response 7 pages ☐ Notice of Appeal/Brief
- ☐ Petition for Extension of Time plus 2 copies ☐ Resp. to Rest. Req. ___ pgs.
- ☐ Issue Fee Trans. (Part B) + 1 copy ☐ Req. to Correct Filing Recpt
- ☐ Copy of Notice to File Missing Parts ☐ Copy of Filing Receipt
- ☐ Request for Nonpublication (1 pg) ☐ Correct Defects ___ pages
- ☒ Authorization to Charge Dep. Acct. # 19-2570 ☒ Postcard
- ☐ _____

17302 U.S. PTO 10/719211 112103

UTILITY PATENT APPLICATION TRANSMITTAL

(For new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No. P50383D2

First Named Inventor Burch, et al

OIPE
AUG 11 2004
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"EXPRESS MAIL CERTIFICATE"

"EXPRESS MAIL" MAILING LABEL NUMBER EV349425397US DATE OF DEPOSIT: 21 November 2003

I hereby certify that this paper or fee and the papers indicated as being transmitted herewith are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date and with the Mailing Label Number indicated above and addressed to: COMMISSIONER FOR PATENTS, MAIL STOP: PATENT APPLICATION, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

NAME OF PERSON MAILING PAPER OR FEE (TYPE OR PRINT) ARLENE CONNOR SIGNATURE Arlene Connor

APPLICATION ELEMENTS *See MPEP chapter 600 concerning utility patent application contents.*	
1. ☒ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to Deposit Account No. 19-2570 ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extensions of time, relating to this application. (37 CFR 1.136(a)(3)) *(Submit an original, and a duplicate for fee processing)*	7. ☒ The Title of the Invention: Pharmaceutical Formulation 8. ☐ Nucleotide and/or Amino Acid Sequence Submission a. ☐ Computer Readable Copy b. ☐ Paper Copy (identical to computer copy) c. ☐ Statement verifying identity of above copies d. ☐ Use the identical computer-readable form filed in Application No. _____, filed ___ _ as the computer-readable form for the instant application. (37 CFR 1.821(e))
2. ☒ The total fee is calculated as shown below: Basic Filing fee $750.00 Total Claims 28 - 20 = 8 x $18 $144.00 Independent Claims 2 -3 = 0 x $86 $ 0.00 ☐ Multiple Dependent Claim present. $290 **TOTAL FILING FEE** **$894.00** ☐ Cancel in this application original claims 1 to 15 of the prior application before calculating the filing fee. ☒ Charge $894.00 to the above indicated Deposit Account.	ACCOMPANYING APPLICATION PARTS 9. a. ☒ Information Disclosure Statement (IDS) b. ☒ PTO-1449 c. ☒ Copies of all IDS Citations 10. ☐ Assignment Papers (cover sheet & document(s)) 11. ☒ Prior Application is Assigned to: SmithKline Beecham p.l.c. *(for continuation/divisional with Box 17a completed*
3a. ☒ Specification excluding Drawings [*Total Pages*] 11 3b. ☒ Abstract on a separate sheet [*Total Pages*] 1	12. ☒ Preliminary Amendment [*Total Pages*] 7
4. ☒ Drawing(s) (35 USC 113) [*Total Sheets*] 3	13. ☒ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
5. ☒ Declaration and Power of Attorney [*Total Pages*] 3 a. ☐ Newly executed (original or copy) b. ☒ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 17a completed)* c. ☐ Unsigned Declaration *[Note Box 6 below]* i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).	14. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)* 15. ☐ Transfer all references cited by Applicants or by the Examiner from the parent Application Serial No. _____ filed_____. A PTO-1449 listing the references is enclosed. 16. ☐ Other: _____
6. ☒ Incorporation By Reference *(useable if Box 5b is checked)* The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 5b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.	

17.	☒ Priority Information, *check appropriate box and supply the requisite information*
a.	The accompanying application is a ☐ Continuation ☒ Divisional ☐ Continuation-in-part (CIP) of prior application No: 09/788,948 filed 20 February 2001 (allowed), which is a divisional of application No. 08/722,259 filed 27 October 1997 (allowed), which is the § 371 national stage filing of PCT/US96/14554 filed 5 September 1996.
b.	☒ Benefit is claimed under Title 35, United States Code, Section 119(e) of the following Provisional Applications: Application No. 60/003,353 filed 7 September 1995.
c.	

Correspondence Address:	GLAXOSMITHKLINE Corporate Intellectual Property - UW2220 P.O. Box 1539 King of Prussia, PA 19406-0939	Signature Name	Respectfully Submitted, Dara L. Dinner
Telephone	(610) 270-5017 *Fax* (610) 270-5090	Registration No.	33,680

20462

PATENT TRADEMARK OFFICE

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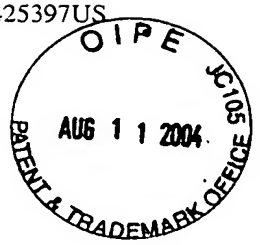

Attorney Docket No. P50383D2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Burch
Divisional of Serial No.: 09/788,948 Previous Art Unit.: 1614
Filed: Herewith Previous Examiner: D. Jagoe
For: PHARMACEUTICAL FORMULATION

Commissioner of Patents
Mail Stop Patent Application
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Dear Sir:

Preliminary to calculation of the filing fees and examination of the above noted application, entrance of the following remarks and amendments into the record is respectfully requested.

Sir:

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 6 of this paper.

The **Abstract** is attached as a separate page.

Amendments to the Specification

Please add the following paragraph to page 1, directly under the title of the invention:

This application is a divisional of Application No. 09/788,948 filed 20 February 2001 (allowed), which is a divisional of Application No. 08/722,259 filed 27 October 1997 (allowed), which is the §371 national stage filing of PCT/US96/14554 filed 5 September 1996 which claims benefits of provisional application 60/003,353 filed 7 September 1995.

Amendments to the Claims:

Claims 1 to 15 cancelled.

16.(new) A container comprising a powder or granular product for reconstitution into a suspension or solution upon the addition of water prior to use, said product comprising amoxycillin and clavulanate, wherein the concentration of the amoxycillin in the reconstituted suspension or solution is about 600mg/5ml and the ratio of amoxycillin to clavulanate is 14:1 +/ 5%.

17.(new) The container as claimed in claim 16 wherein the amount of clavulanate is about 43mg/5ml.

18.(new) The container as claimed in claim 16 where upon the addition of water contains about 100ml reconstituted suspension or solution.

19.(new) The container as claimed in claim 16 in which amoxycillin is in the form of amoxycillin trihydrate.

20.(new) The container as claimed in claim 16 in which amoxycillin is in the form of crystalline sodium amoxycillin.

21.(new) The container as claimed in claim 16 in which clavulanate is in the form of potassium clavulanate.

22.(new) The container as claimed in claim 16 which further comprises an edible desiccant.

23.(new) The container as claimed in claim 22 wherein the desiccant is silicon dioxide.

24.(new) The container as claimed in claim 16 which further comprises at least one of a diluent, a suspending agent, a glidant, a bulking agent, a flavour, a sweetener and a stabilizer.

25.(new) The container as claimed in claim 24 wherein the suspending agent is xanthan gum and hydroxypropylmethyl cellulose, or a mixture thereof; the glidant is

colloidal silica; the stabilizer is succinic acid; the sweetener aspartame; and the bulking agent is silicon dioxide.

26.(new) The container as claimed in claim 24 wherein the flavour is selected from banana, raspberry, orange, golden syrup, or mixtures thereof.

27.(new) The container as claimed in claim 16 wherein the reconstituted solution is a flavoured aqueous syrup.

28.(new) The container as claimed in claim 16 which comprises the reconstituted suspension or solution.

29.(new) The container as claimed in claim 16 which is moisture proof.

30.(new) A container comprising a powder or granular product for reconstitution into a suspension or solution upon the addition of water prior to use, said product comprising amoxycillin and clavulanate, wherein the concentration of clavulanate when reconstituted is from about 35 to 50mg/5ml and the ratio of amoxycillin to clavulanate is 14:1 +/ 5%.

31.(new) The container as claimed in claim 30 wherein the amount of clavulanate in the product is about 43mg/5ml.

32.(new) The container as claimed in claim 30 wherein the amount of amoxycillin in the product is from about 500 to 700mg/5ml.

33.(new) The container as claimed in claim 30 where upon the addition of water contains 100ml reconstituted suspension or solution.

34.(new) The container as claimed in claim 30 in which the amoxycillin in the product is in the form of amoxycillin trihydrate.

35.(new) The container as claimed in claim 30 in which the amoxycillin in the product is in the form of crystalline sodium amoxycillin.

36.(new) The container as claimed in claim 30 in which the clavulanate in the product is in the form of potassium clavulanate.

37.(new) The container as claimed in claim 30 which product further comprises an edible desiccant.

38.(new) The container as claimed in claim 37 wherein the desiccant is silicon dioxide.

39.(new) The container as claimed in claim 301 which product further comprises at least one of a diluent, a suspending agent, a glidant, a bulking agent, a flavour, a sweetener and a stabilizer.

40.(new) The container as claimed in claim 39 wherein the suspending agent is xanthan gum and hydroxypropylmethyl cellulose, or a mixture thereof; the glidant is colloidal silica; the stabilizer is succinic acid; the sweetener aspartame; and the bulking agent is silicon dioxide.

41.(new) The container as claimed in claim 30 wherein the reconstituted solution is a flavoured aqueous syrup.

42.(new) The container as claimed in claim 39 wherein the flavour is selected from banana, raspberry, orange, golden syrup, or mixtures thereof.

43.(new) The container as claimed in Claim 30 which is moisture proof.

REMARKS

Claims 16 to 43 are in the application. Claims 1 to 15 have been cancelled.

Support for the newly added claims lies in the specification on page 2, lines 13 to 15, 19 to 24, and 25 to 38; and page 3, lines 15 to 20. No new matter is believed added.

An abstract on a separate sheet of paper accompanies this request.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

Dara L. Dinner
Attorney for Applicant
Registration No. 33,680

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n:\dld\oa\us\50383\d2\prelimamend.doc

ABSTRACT

Pharmaceutical formulations comprising amoxycillin and clavulante in a ratio of from 10:1 to 20:1 are of use in the emperic treatment of infections potentially caused by DRSP.

Docket No.: P50383X2D1

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"PHARMACEUTICAL FORMULATION"

the specification of which (check one)
[ ] is attached hereto.
[X] was filed on 20 February 2001 as Serial No. 09/788,948
and as presently amended on 18 June 2003.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date
60/003,353	7 September 1995

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status
PCT/US96/14454	5 September 1996	Inactive
08/722,259	27 October 1997*	Allowed

*date granted per petition

Address all correspondence and telephone calls to **Customer Number 20462**
Dara L. Dinner, GlaxoSmithKline, CIP-U.S., UW2220, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939, whose telephone number is 610-270-5017.

I hereby appoint the practitioners associated with the Customer Numbers provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith Customer Number 20462 and Customer Number 23347.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: Daniel Joseph Burch

Inventor's Signature: _____

Date: 5 Sept 03

Residence: Oaks, Pennsylvania

Citizenship: United States of America

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Corporate Intellectual Property - UW2220
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King of Prussia, Pennsylvania 19406-0939

Full Name of Inventor: Phillip M. John

Inventor's Signature: _____

Date: 8/28/03

Residence: Bristol, Tennessee

Citizenship: United States of America

Post Office Address: GlaxoSmithKline
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Full Name of Inventor: Michael G. Ramsey

Inventor's Signature: Michael G. Ramsey

Date: 02 Sept. 03

Residence: Bristol, Tennessee

Citizenship: United States of America

Post Office Address: GlaxoSmithKline
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Full Name of Inventor: Harvey L. Zimmerman

Inventor's Signature: Harvey L. Zimmerman

Date: 28 Aug 03

Residence: Bristol, Tennessee

Citizenship: United States of America

Post Office Address: GlaxoSmithKline
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

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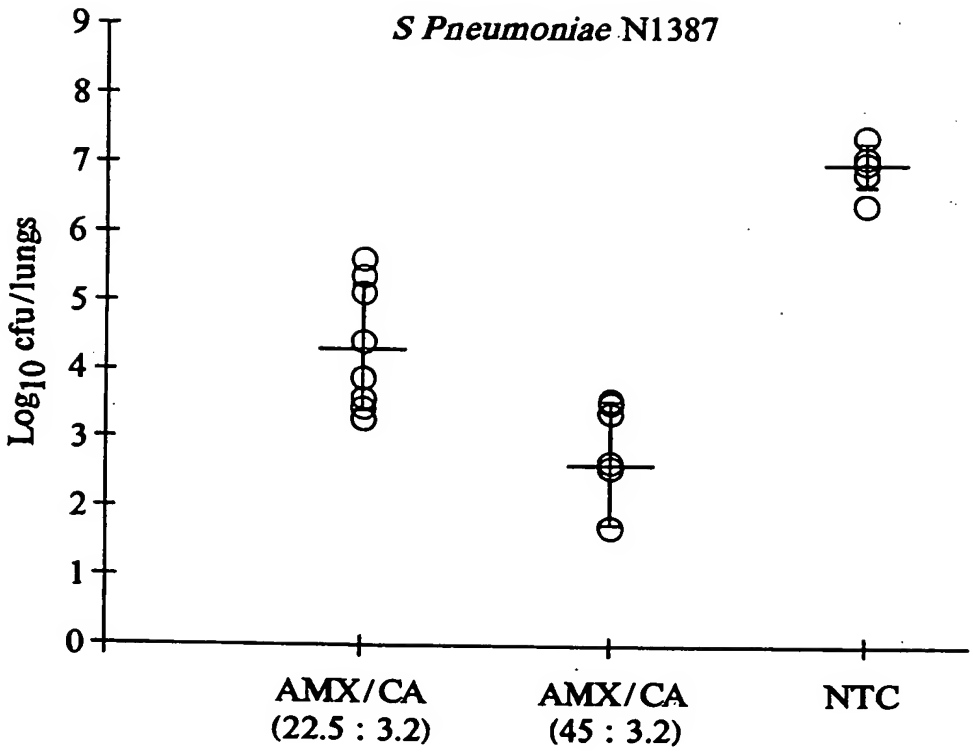

FIG. 1

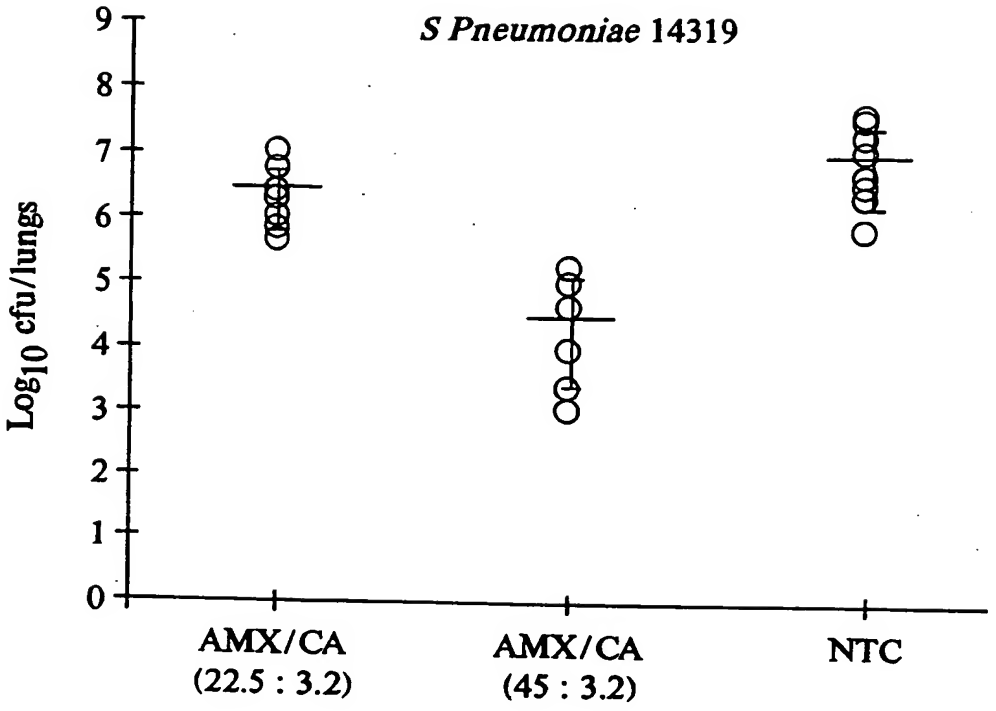
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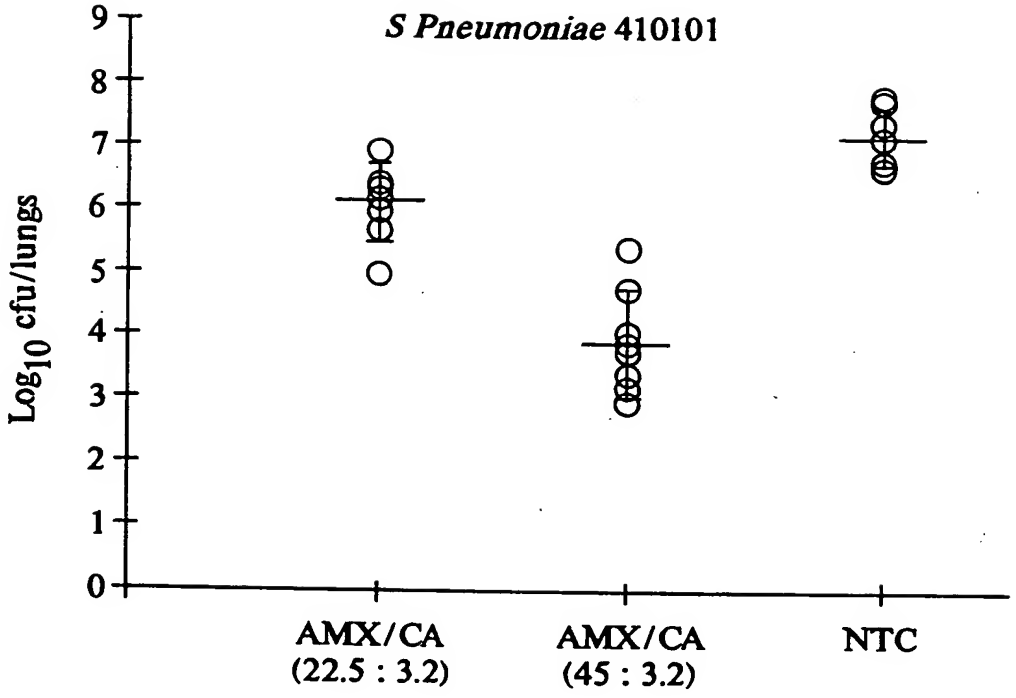
FIG. 2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AMX/CA
(45 : 3.2)
NTC

FIG. 3

Form PTO-1449 U.S. Department of Commerce Patent and Trademark Office	ATTY. DOCKET NO. P50383X2D1	SERIAL NO. 09/788,948
INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use several sheets if necessary)*	APPLICANT Burch	
	FILING DATE 20 February 2001	GROUP Unknown

OIPE JC10 AUG 1 1 2004 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
	4,525,352	6/25/85	Cole et al.			
	4,282,202	8/4/81	Dowrick			
	4,301,149	11/17/81	Crowley			
	4,441,609	4/10/84	Crowley			
	4,537,887	8/27/85	Rooke et al.			
	4,673,637	6/16/87	Hyman			
	5,733,577	3/31/98	Myers et al.			
	6,051,255	4/18/00	Conley et al.			
	6,077,536	6/20/00	Merrifield et al.			
	5,962,022	10/5/99	Bolt et al.			

FOREIGN PATENT DOCUMENTS

	Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
	WO 95/20946	8/10/95	WIPO				
	WO 94/16696	8/4/94	WIPO				
	0 080 862	11/25/82	EPO				
	1 044 680 A1	10/18/00	EPO				
	2 005 538	4/25/79	Great Britain				
	WO 00/12088	3/9/00	WIPO				
	WO 91/15197	10/17/91	WIPO				
	WO 92/19227	11/12/92	WIPO				
	WO 93/00898	1/21/93	WIPO				
	WO 94/27557	12/8/94	WIPO				
	WO 94/27600	12/8/94	WIPO				
	WO 95/28148	10/26/95	WIPO				
	WO 95/28927	11/2/95	WIPO				
	WO 96/04907	2/22/96	WIPO				
	WO 96/34605	11/7/96	WIPO				
	WO 97/09042	3/13/97	WIPO				
	WO 98/35672	8/20/98	WIPO				
	WO 98/40054	9/17/98	WIPO				

Form PTO-1449 U.S. Department of Commerce Patent and Trademark Office	ATTY. DOCKET NO. P50383D2	DIV. OF SERIAL NO. 09/788,948
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	APPLICANT Burch	
(Use several sheets if necessary)	FILING DATE Herewith	GROUP Unknown

	WO 98/42311	10/1/98	WIPO				
	EP 0281200A	2/26/88	EPC				
	EP 0389177A	3/15/90	EPC				
	HU 205611B	4/29/91	Hungary				
	WO 95/25516	9/28/95	WIPO				
	WO 95/33487	12/14/95	WIPO				
	WO 96/04908	2/22/96	WIPO				
	WO 96/07408	3/14/96	WIPO				
	WO 00/03695	1/27/00	WIPO				
	WO 98/07424	02/26/98	WIPO				

OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*

	Bottenfield et al., "Safety and Tolerability of a New Formulation...in the Empiric Treatment of Pediatric...*Streptococcus pneumoniae*", Pediatric Infect. Dis. J., Vol. 17, pp. 963-968 (1998)
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(54) Title: PHARMACEUTICAL FORMULATION

(57) Abstract

Pharmaceutical formulations comprising amoxycillin and clavulanate in a ratio of from 10:1 to 20:1 are of use in the emperic treatement of infections potentially caused by DRSP.

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Pharmaceutical Formulation

This invention relates to pharmaceutical formulations comprising amoxycillin and a salt of clavulanic acid (hereinafter termed "clavulanate" unless a specific salt is identified).

The combination of amoxycillin and clavulanate is an effective empirical treatment for bacterial infections and may be administered by oral dosing, for instance in the form of tablets, and, for paediatric formulations, aqueous solutions or suspensions, typically as a flavoured syrup.

Clavulante is a β-lactamase inhibitor and is included with the β-lactam antibiotic amoxycillin to counter a β-lactamase mediated resistance mechanism. Some microrganisms such as *Streptococcus pneumoniae* have resistance mechanisms which are not β-lactamase mediated. WO94/16696 discloses generally that potassium clavulanate may enhance the effectiveness of beta-lactam antibiotics such as amoxycillin against microorganisms having a resistance mechanism which is not β-lactamase mediated.

Streptococcus pneumoniae is an important pathogen in respiratory tract infection in the community. *S pneumoniae* is the most commonly implicated bacterium in the important respiratory tract infections of otitis media in paediatrics and sinusitis in patients of all ages and acute exacerbations of bronchitis and pneumococcal pneumonia in adults. There have been increasing reports in Europe and the US of the emergence of DRSP (drug-resistant *Streptococcus pneumoniae*) with decreased suspectibility to β-lactam and other antibiotics.

Whilst confirmed cases of DRSP infection may be successfully treated with relatively high levels of amoxycillin, there still remains the need to develop effective empiric treatments, where DRSP may be suspected, for instance in an area with a high prevalence of DRSP, but where other, β-lactamase producing, organisms may also be present.

It has now been found that empiric treatment of infections potentially caused by DRSP may be successfully treated with formulations of co-amoxiclav which have a relatively large amount of amoxycillin.

Accordingly, the present invention provides a pharmaceutical formulation adapted for oral administration comprising amoxycillin and clavulanate in a weight ratio between 10:1 and 20:1 inclusive in combination with a pharmaceutically acceptable carrier or excipient.

Such formulations are of use for the empiric treatment of infections, potentially caused by DRSP, in particular respiratory tract infections such as otitis

media in paediatrics and sinusitis in patients of all ages and acute exacerbations of bronchitis and pneumococcal pneumonia in adults

The invention also provides for the use of amoxycillin and clavulanate in a ratio of between 10:1 and 20:1 inclusive in the manufacture of a medicament for oral administration for the empiric treatment of infections potentially caused by DRSP in human patients.

The invention also provides a method for the empiric treatment of infections potentially caused by DRSP in a human patient comprising the oral administration to a patient in need thereof of a pharmaceutical formulation comprising amoxycillin and clavulanate in a weight ratio between 10:1 and 20:1 inclusive.

The formulations of the present invention are suitable for use with patients of all ages, including adult, older children and and paediatric patients.

The weight ratios of amoxycillin:clavulanate expressed herein are as free acid equivalent. Preferred amoxycillin:clavulanate ratios are between 12:1 to 16:1 inclusive, especially about 14:1 ± 5%.

In the formulations of the invention the amoxycillin is preferably in the form of amoxycillin trihydrate, although sodium amoxycillin, for example the crystalline form of sodium amoxycillin which is disclosed in EP 0131147 A may also be used.

Clavulanate is preferably in the form of potassium clavulanate. Potassium clavulanate is extremely moisture-sensitive and should be stored and handled in conditions of 30% RH or less, ideally as low as possible. Solid dosage forms should be packaged in atmospheric moisture-proof containers, and such forms and/or their containers may contain a desiccant.

The formulations of the invention may be made up into solid dosage forms for oral administration by a method conventional to the art of pharmaceutical technology, e.g. tablets or powder or granular products for reconstitution into a suspension or solution. Suitable ingredients and suitable methods for making such tablets are disclosed in for example GB 2 005 538-A, WO 92/19227 and WO 95/28927. Powder or granular formulations, such as paediatric suspension formulations, may be manufactured using techniques which are generally conventional in the field of manufacture of pharmaceutical formulations and in the manufacture of dry formulations for reconstitution into such suspensions. For example a suitable technique is that of mixing dry powdered or granulated ingredients for loading into a suitable container.

For paediatric dosing, the formulations of the invention are preferably made up into a sweet flavoured aqueous syrup formulation of generally conventional formulation (except for its novel amoxycillin : clavulanate ratio and intended use) containing a suitable weight of the amoxycillin and clavulanate in a unit dose volume,

e.g. 5 ml or 2.5 ml of the syrup. Because of the water-sensitivity of clavulanate it is preferred to provide such a syrup formulation as dry powder or granules contained in an atmospheric moisture-proof container or sachet for make up with water or other suitable aqueous medium shortly prior to use.

The formulation of this invention will normally, in addition to its active materials amoxycillin trihydrate and potassium clavulanate, also include excipients which are standard in the field of formulations for oral dosing and used in generally standard proportions, and at generally standard particle sizes and grades etc.

In the case of paediatric oral suspensions, these excipients may comprise suspending aids, glidants (to aid filling), diluents, bulking agent, flavours, sweeteners, stabilisers, and in the case of dry formulations for make up to an aqueous suspension, an edible desiccant to assist preservation of the potassium clavulanate against hydrolysis by atmospheric moisture on storage. Potassium clavulanate is normally supplied in admixture with silicon dioxide as diluent.

Suitable excipients for use include xantham gum (suspension aid), colloidal silica (glidant), succinic acid (stabiliser), aspartame (sweetener), hydroxypropyl-methylcellulose (suspension aid) and silicon dioxide (desiccant, diluent for potassium clavulanate and bulking agent). Flavours may comprise common flavours such as orange, banana, raspberry and golden syrup, or mixtures thereof, to suit local requirements.

Generally the proportion of active materials amoxycillin trihydrate and potassium clavulanate in a dry formulation for make up with aqueous media into a solution, suspension or syrup formulation of the invention may be around 30-80 wt%.

The present invention therefore also provides a process for manufacture of a formulation as described above.

The formulations of the invention may be adapted to paediatric dosing, i.e. to patients aged between 3 months to 12 years. Such formulations may be dosed in daily quantities up to the maximum normal permitted dose of amoxycillin and clavulanate.

A suitable dosage quantity of the formulation of the invention for paediatric patients is 75 to 115 mg/kg amoxycillin per day and 5 to 7.5 mg/kg of clavulanate per day. Suitably, the dosage is administered bid, for example in two, preferably equal, unit doses per day, suitably around 12 hours apart. A suitable dosage for use in such a regimen is 90±10%, especially ±5%, mg/kg amoxycillin and 6.4±10%, especially ± 5%, mg/kg clavulanate (i.e. nominally a 14:1 ratio) per day.

Suitably, paediatric formulations as hereinbefore described are provided which comprise from 500 to 700, preferably about 600mgof amoxycillin/5ml of

formulation when reconstituted and from 35 to 50 mg, preferably about 43mg of clavulanic acid/5ml of formulation when reconstituted.

For older children and adult patients these quantities may be increased *pro rata*. A suitable dosage for use in such a regimen is 3500±10%, especially ±5%, mg amoxycillin and 250±10%, especially ±5%, mg clavulanate (i.e. nominally a 14:1 ratio) per day, preferably administered bid, for example in two, preferably equal, unit doses per day, suitably around 12 hours apart

The formulation of the invention may for example be provided in solid unit dose forms embodying suitable quantities for the administration of such a daily dose. For example a unit dosage form may be tablets, or sachets containing granules or powders for reconstitution, one or two of which are to be taken at each bid dosing interval. Alternatively a unit dose may be provided as a bulk of solid or solution or suspension, e.g. as a syrup for paediatric administration, together with a suitable measuring device of known type to facilitate administration of a suitable unit dose quantity of the formulation. A suitable unit dose quantity is one which enables the administration of the above-mentioned daily dosage quantity divided between two bid doses.

For paediatric patients, a suitable unit dose quantity is preferably one which enables the administration of the above-mentioned daily dosage quantity, divided between two bid doses, e.g. half of the above-mentioned daily dose, in a volume of a solution or suspension suitable for oral administration to a paediatric patient, preferably of between 2.5 to 10 ml, preferably as a syrup. A paediatric formulation may therefore comprise a bulk of a solution or suspension, e.g. a syrup, or granules or powder which can be made up into such a solution or suspension, at a concentration of solution or suspension which contains such a dose in such a volume.

The present invention therefore also provides the above described formulation provided for administration in such doses.

For adults, a suitable unit dose may be provided in a tablet. Suitably, for a bid dosage regimen based on 1750mg amoxycillin/125mg clavulanate per unit dose, this may conveniently be provided as two tablets, one comprising amoxycillin and clavulanate and a second comprising amoxycillin alone. Accordingly, in a further aspect, the present invention provides for a unit dosage of 1750mg amoxycillin and 125mg clavulante provided by two tablets, one comprising 875mg amoxycillin and 125mg clavulanate and a second comprising 875mg amoxycillin. A suitable tablet comprising 875mg amoxycillin and 125mg clavulanate is marketed by SmithKline Beecham in several countries and is also described in WO 95/28927 (SmithKline Beeecham).

The invention will now be described by way of example only with reference to Figs. 1, 2 and 3 which show graphically the results of Example 3 below.

Figs. 1, 2 and 3 show respectively Log_{10} of colony forming units ("cfu") of *S Pneumoniae* strains N1387, 14319 and 410101 per lungs observed in rats following dosing with an amoxycillin : potassium clavulanate ("AMX : CA") formulation of this invention administered at 45 : 3.2 mg/kg amoxycillin : clavulanic acid equivalent, a comparison formulation administered at 22.5 : 3.2 mg/kg, and a non-treated control ("NTC") as described below.

Example 1 - Paediatric formulation

The following paediatric formualtion comprising 600mg amoxicillin and 42.9mg clavulanic acid in 5ml of suspension when reconstituted:

Ingredient	**Quantity (mg)**
Amoxycillin trihydrate	697.00*
(equivalent to amoxicillin free acid)	600.00
Potassium Clavulanate/Syloid 1:1 blend	113.00**
(equivalent to clavulanic acid, including 8% overage)	46.332
Xanthan Gum	12.500
Aspartame	12.500
Succinic acid	0.835
Colloidal silicon dioxide	25.00
Hydroxypropyl methyl cellulose	79.650
Flavours	72.500
Silicon dioxide	86.315***
Total fill weight	**1100.00**

* based on 86% potency as amoxicillin free acid

** based on 41% potency as clavulanic acid in potassium clavulante/Syloid 1:1 blend, including an 8% overage

*** quantity of silicon dioxide (Syloid) varies, according to quantities of amoxycillin trihydrate and potassium clavulanate/Syloid blend, such that total fill weight remains constant at 1100.00mg

Bottles are filled with 23.92g of formulated powder and then reconstituted with 84 ml of water immediately prior to use, to give 100ml of suspension.

Example 2 - Tablet Formulation

A tablet formulation comprising 875mg amoxycillin and 125mg clavulanate was prepared having the following composition:

Ingredient	(mg.)	wt.%
Active Constituents:		
Amoxycillin trihydrate	1017.4	70.2
(equivalent to amoxycillin)	875.00	
Potassium clavulanate	152.45	10.5
(equivalent to clavulanic acid)	125.0	
Other Constituents:		
Magnesium Stearate	14.50	1.00
Sodium Starch Glycollate	29.00	2.00
Colloidal Silicon Dioxide	10.0	0.70
Microcrystalline Cellulose	226.65	15.6
Core tablet weight	**1450.00**	**100.00**

The tablets are made by blending the amoxycillin, potassium clavulanate, and portions of microcrystalline cellulose and magnesium stearate, roller compacting this blend, then blending with the other constituents, before tabletting on a conventional tablet press and coating. The tablet core is coated with a film (Opadry White YS-1-7700/Opadry White OY-S-7300 ex Colorcon) from an aqueous solvent system, to give tablets with a nominal coated weight of 1482mg. Further details of how the tablets are manufactured are provided in WO 95/28927 (SmithKline Beecham).

Similar tablets can be made in which the roller compaction step is replaced by slugging and /or a final film coating is applied from an organic solvent system such as dichloromethane rather than an aqueous solvent system.

A tablet formulation comprising 875mg amoxycillin was prepared havig the following composition:

Core components (mg/tablet)	
Amoxicillin trihydrate	1017.4 (875 fa)
Crospovidone, NF	30.5
Microcrystalline cellulose, NF	204.4
Sodium starch glycollate, NF	26.0
Colloidal Silicon Dioxide, NF	8.7
Magnaesium stearate, NF	13.0
Film Coat	
Opadry Pink	39.0

The tablets are made by blending the amoxycillin and portions of microcrystalline cellulose and magnesium stearate, roller compacting this blend, then blending with the other constituents, before tabletting on a conventional tablet press and coating.

Example 3 - Biological Data - In vivo Rat model:

Methodology.

Animals were anaesthetised and the external jugular vein was cannulated for administration of compounds. At least 48h later animals were infected by intra-bronchial instillation of a 50 microlitre inoculum of *S Pneumoniae* by non surgical intubation. Inocula were prepared in cooled molten nutrient agar with a final inoculum of approximately 10^6cfu in 50 microlitres of agar.

Dosing commenced 24h after infection and compounds were administered as a continuous infusion into the jugular vein designed to simulate in rat plasma the concentration versus time curves obtained in human serum following oral administration of amoxycillin / clavulanate. For each organism tested, three groups of animals were used. The first two groups received amoxycillin and clavulanate to simulate bid dosing of this combination at either 22.5/3.2 mg/kg (a 7:1 ratio) or 45/3.2 mg/kg (a 14:1 ratio) to children. The remaining group received an infusion of saline at a rate similar to the dosed groups and acted as infected non-treated controls. Dosing continued for 2-5 days, and 14 days after therapy ended the animals were killed and lungs removed aseptically for bacteriological assessment.

Results

Table 1 shows the MIC's of amoxycillin, amoxycillin:clavulanate and penicillin G for the three resistant strains of *S Pneumoniae* tested.

Table 1.

Strain	MIC(mcg/ml) Amoxycillin	Amox:clav.	Penicillin G
N1387	2	2	2 (R)
14319	4	4	8 (R)
410101	4	4	4 (R)

***Streptococcus Pneumoniae* N1387:**

Bacterial numbers in the lungs of saline-treated animals were 6.97±0.30 $\log_{10}$ cfu/lungs. Both doses of amoxycillin : clavulanate reduced the numbers of viable bacteria in the lungs significantly compared with control animals (4.37±0.93 $\log_{10}$ cfu/lungs and 2.62+0.85 $\log_{10}$ cfu/lungs for the 7 : 1 and 14 : 1 ratios respectively; $p<0.01$). However as shown in Fig. 1 amoxycillin : clavulanate at the 14 : 1 bid ratio was significantly more effective than when administered at the lower ratio of 7:1.

***Streptococcus Pneumoniae* 14319:**

Bacterial numbers in the lungs of saline-treated animals were 6.8±0.62 $\log_{10}$ cfu/lungs. Amoxycillin : clavulanate at the 7:1 ratio reduced the numbers of viable bacteria in the lungs (6.26±0.47 $\log_{10}$ cfu/lungs) but this reduction did not reach significance compared with control animals. However as shown in Fig. 2 amoxycillin : clavulanate at the 14 : 1 ratio bid reduced the bacterial count to 4.28±0.82 $\log_{10}$ cfu/lungs such that this dose was significantly more effective than control animals and animals treated with the lower ratio of 7:1.

***Streptococcus Pneumoniae* 410101.**

Bacterial numbers in the lungs of saline-treated animals were 7.11±0.45 $\log_{10}$ cfu/lungs. Amoxycillin : clavulanate at the 7:1 ratio reduced the numbers of viable bacteria in the lungs (6.14±0.6 $\log_{10}$ cfu/lungs) significantly compared with control animals (p,0.05). However as shown in Fig. 3 amoxycillin : clavulanate at the 14 : 1 ratio bid reduced the counts to 3.91±0.81 $\log_{10}$ cfu/lungs and was significantly more effective than animals treated with the lower ratio of 7:1.

Claims

1. A pharmaceutical formulation comprising amoxycillin and clavulanate in a weight ratio between 10 : 1 and 20 : 1 inclusive.

2. A formulation as claimed in claim 1 in which the ratio of amoxycillin to clavulante is between 12 : 1 and 16 : 1 inclusive.

3. A formulation as claimed in claim 1 in which the ratio of amoxycillin to clavulante is about 14 : 1.

4. A formulation as claimed in any one of claims 1 to 3 in which amoxycillin is in the form of amoxycillin trihydrate.

5. A formulation as claimed in any one of claims 1 to 4 in which clavulanate is in the form of potassium clavulanate.

6. A formulation as claimed in any one of claims 1 to 5 adapted for administration to paediatric patients in the form of a powder or granular product for reconstitution into a suspension or solution and which comprises from 500 to 700mg/5ml of amoxycillin and from 35 to 50mg/5ml of clavulanate when reconstituted.

7. A formulation as claimed in any one of claims 1 to 5 in the form of tablets and adapted to provide about 1750mg amoxycillin and 125mg clavulanate per unit dose.

8. A formulation as claimed in claim 7 comprising a first tablet comprising 875mg amoxycillin and 125mg clavulanate and a second tablet comprising 875mg amoxycillin.

9. A process for preparing a pharmaceutical formulation according to any one of the preceding claims which process comprises admixing the ingredients thereof in any order that is convenient.

10. The use of amoxycillin and clavulanate in a ratio of between 10:1 and 20:1 inclusive in the manufacture of a medicament for oral administration for the empiric treatment of infections potentially caused by DRSP in human patients.

11. A method for the empiric treatment of infections potentially caused by DRSP in a human patient comprising the oral administration to a patient in need thereof of a pharmaceutical formulation comprising amoxycillin and clavulanate in a weight ratio between 10:1 and 20:1 inclusive.

12. A method as claimed in claim 11 in which the dosage quantity for paediatric patients is 75 to 115 mg/kg amoxycillin per day and from 5 to 7.5 mg/kg of clavulanate per day.

13. A method as claimed in claim 12 in which the dosage quantity is 90±10% mg/kg amoxycillin and 6.4±10% mg/kg clavulanate.

14. A method as claimed in claim 11 in which the dosage amount for an older child or an adult patient is 3500±10% mg amoxycillin and 250±10% mg clavulanate.

15. A method as claimed in claim 13 or claim 14 in which the dosage is administered bid.

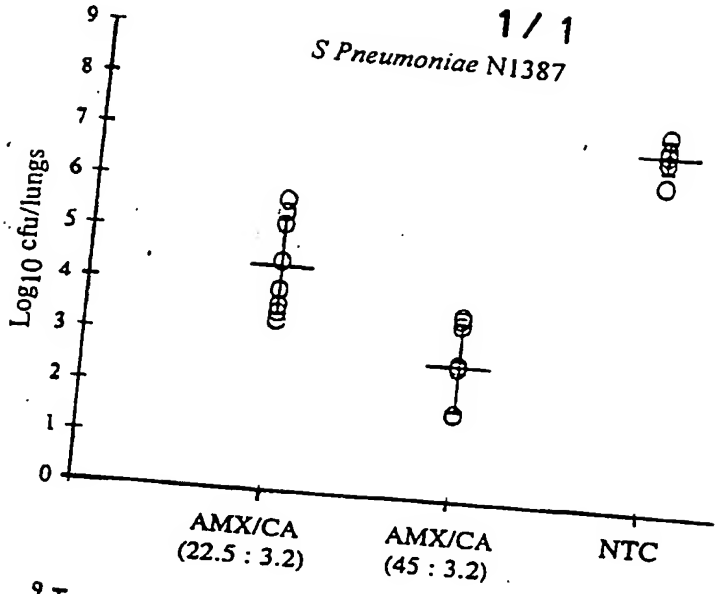

Fig. 1

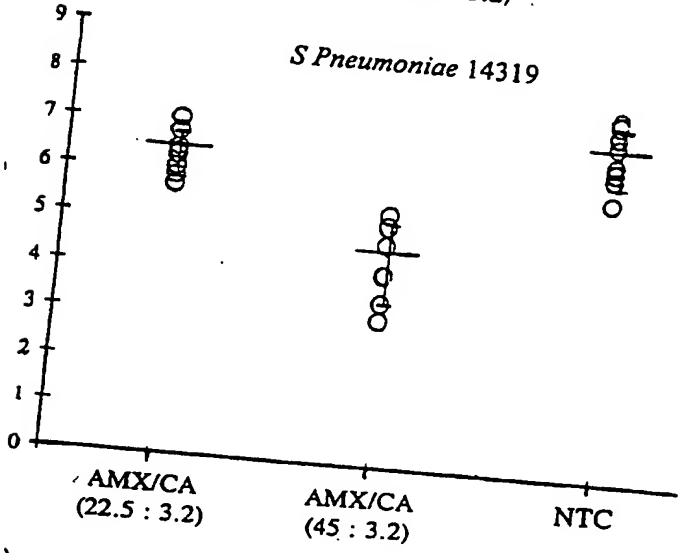

Fig. 2

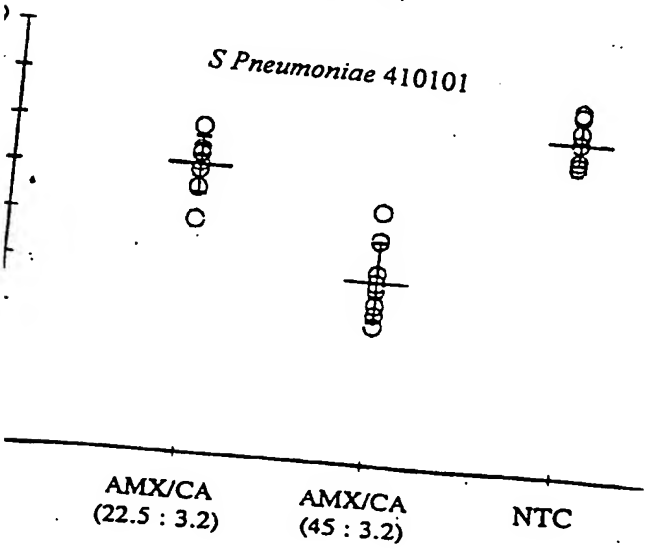

Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/14554

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/43, 31/395
US CL :514/197, 210

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/197, 210

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 4,525,352 A (COLE ET AL.) 25 June 1985, column 1, lines 28-63, column 7, lines 61-65 and column 9, lines 5-11 and 27-37.	1-4 and 10 --- 11-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 OCTOBER 1996	Date of mailing of the international search report 06 NOV 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RAYMOND J. HENLEY III Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/14554

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-9
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.